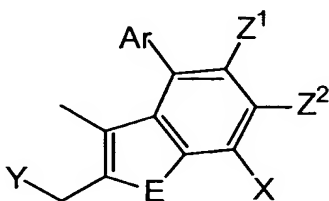


WHAT IS CLAIMED:

1. A method for treatment of Syndrome X or type II diabetes in a mammal, the method comprising administering to a mammal in need thereof:

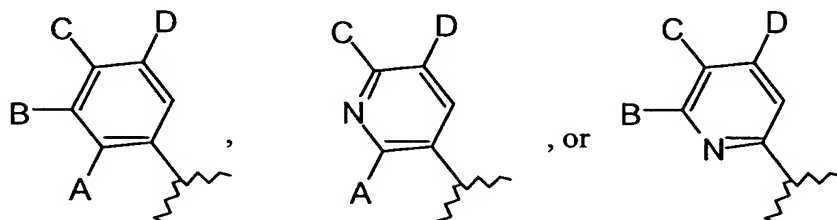
- 5 a) a pharmaceutically effective amount of a biguanide agent; and
 b) a pharmaceutically effective amount of a PTPase inhibiting compound of formula I:



(I)

wherein

10 Ar is



A is hydrogen, halogen, or OH;

B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, hydroxyalkyl of 1-6 carbon atoms,
 15 hydroxyaralkyl of 6-12 carbon atoms, cycloalkyl of 3-8 carbon atoms, nitro, amino, $-NR^1R^{1a}$, $-NR^1COR^{1a}$, $-NR^1CO_2R^{1a}$, cycloalkylamino of 3-8 carbon atoms, morpholino, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, $-COR^{1b}$ or OR;

R is hydrogen, alkyl of 1-6 carbon atoms, $-COR^1$, $-(CH_2)_nCO_2R^1$, $-CH(R^{1a})CO_2R^1$,
 20 $-SO_2R^1$, $-(CH_2)_mCH(OH)CO_2R^1$, $-(CH_2)_mCOCO_2R^1$, $-(CH_2)_mCH=CHCO_2R^1$, or $-(CH_2)_mO(CH_2)_oCO_2R^1$;

R^1 is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, aryl, or $CH_2CO_2R^{1'}$;

$R^{1'}$ is hydrogen or alkyl of 1-6 carbon atoms

E is S, SO, SO₂, O, or NR^{1c};

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, CN, aryl, aralkyl of 6-12 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, hydroxyaralkyl of 6-12 carbon atoms, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy; arylalkoxy, nitro, amino, NR²R^{2a}, NR²COR^{2a}, cycloalkylamino of 3-8 carbon atoms, morpholino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, 2-N,N-dimethylaminoethyl-sulfanyl, -OCH₂CO₂R^{2b} or -COR^{2c};

Y is hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, hydroxyaralkyl of 6-12 carbon atoms, -OR³, SR³, NR³R^{3a}, -COR^{3b}, morpholine or piperidine;

R^{1a}, R^{1c}, R², R^{2a}, R³, R^{3a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or aryl;

R^{1b} is alkyl of 1-6 carbon atoms or aryl;

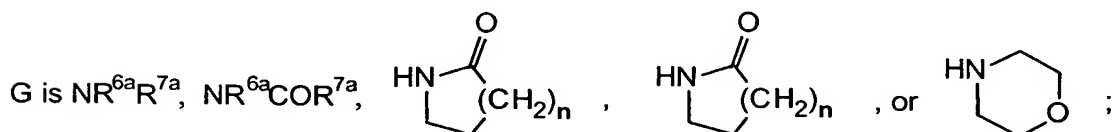
R^{2b} is hydrogen, alkyl of 1-6 carbon atoms;

R^{2c} and R^{3b} are each, independently, alkyl of 1-6 carbon atoms, aryl, or aralkyl of 6-12 carbon atoms;

C is hydrogen, halogen or OR⁴;

R⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R⁵)W, -C(CH₃)₂CO₂R⁶, 5-thiazolidine-2,4-dione, -CH(R⁷)(CH₂)_mCO₂R⁶, -COR⁶, -PO₃(R⁶)₂, -SO₂R⁶, -(CH₂)_pCH(OH)CO₂R⁶, -(CH₂)_pCOCO₂R⁶, -(CH₂)_pCH=CHCO₂R⁶, or -(CH₂)_pO(CH₂)_qCO₂R⁶;

R⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, aryl, -CH₂(1H-imidazol-4-yl), -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), -CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), -CH₂(3-pyridyl), -CH₂CO₂H, or -(CH₂)_nG;



W is CO_2R^6 , CONH_2 , CONHOH , CN , $\text{CONH}(\text{CH}_2)_2\text{CN}$, 5-tetrazole, $-\text{PO}_3(\text{R}^6)_2$,
 $-\text{CH}_2\text{OH}$, $-\text{CONR}^{6b}\text{CHR}^{7b}$, $-\text{CH}_2\text{NR}^{6b}\text{CHR}^{7b}\text{CO}_2\text{R}^6$,
 $-\text{CH}_2\text{OCHR}^{7b}\text{CO}_2\text{R}^6$ $-\text{CH}_2\text{Br}$, or $-\text{CONR}^{6b}\text{CHR}^{7b}\text{CO}_2\text{R}^6$;

R^6 , R^{6a} , R^7 , R^{7a} are each, independently, is hydrogen, alkyl of 1-6 carbon atoms,
 5 or aryl;

R^{6b} is hydrogen or $-\text{COR}^{6c}$;

R^{6c} is alkyl of 1-6 carbon atoms or aryl;

R^{7b} is hydrogen, alkyl of 1-6 carbon atoms, or hydroxyalkyl of 1-6 carbon atoms;

10 Z^1 and Z^2 are each, independently, hydrogen, halogen, CN , alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, cycloalkyl of 3-8 carbon atoms, nitro, amino, $-\text{NR}^1\text{R}^{1a}$, $-\text{NR}^1\text{COR}^{1a}$, cycloalkylamino of 3-8 carbon atoms, morpholino, or OR^8 , or Z^1 and Z^2 may be taken together as a diene unit having the formula $-\text{CH}=\text{CR}^9-\text{CR}^{10}=\text{CR}^{11}-$;

R^8 is hydrogen, alkyl of 1-6 carbon atoms, or aryl;

15 R^9 , R^{10} , and R^{11} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aryl, halogen, hydroxy, or alkoxy of 1-6 carbon atoms

m is 1 to 4

n is 1 or 2;

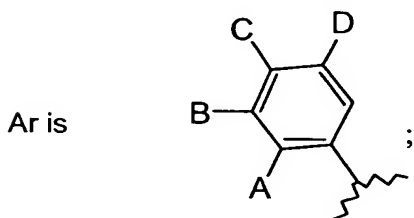
p is 1 to 4;

20 q is 1 to 4;

or a pharmaceutically acceptable salt thereof; and

c) optionally, a pharmaceutically effective amount of a sulfonylurea agent, or a pharmaceutically acceptable salt form thereof.

25 2. The method of Claim 1 wherein the PTPase inhibiting compound is as defined in Claim 1, wherein:



- A is hydrogen or halogen
- B and D are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, branched alkyl, cycloalkyl of 3-8 carbon atoms, nitro or OR;
- 5 R is hydrogen or alkyl of 1-6 carbon atoms;
E is S, or O;
- X is hydrogen, halogen, alkyl of 1-6 carbon atoms, CN, perfluoroalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, aryloxy; arylalkoxy, nitro, amino, NR²R^{2a}, NR²COR^{2a}, cycloalkylamino, morpholino, alkylsulfanyl of 1-6 carbon atoms, arylsulfanyl, pyridylsulfanyl, or 2-N,N-dimethylaminoethylsulfanyl;
- 10 R¹, R^{1a}, R², R^{2a}, R³, and R^{3a} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or aryl;
- Y is hydrogen, halogen, OR³, SR³, NR³R^{3a}, or morpholine;
- 15 C is hydrogen, halogen, or OR⁴;
- R⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R⁵)W, -C(CH₃)₂CO₂R⁶, 5-thiazolidine-2,4-dione, -CH(R⁷)(CH₂)_mCO₂R⁶, -COR⁶, -PO₃(R⁶)₂, -SO₂R⁶, -(CH₂)_pCH(OH)CO₂R⁶, -(CH₂)_pCOCO₂R⁶, -(CH₂)_pCH=CHCO₂R⁶, -(CH₂)_pO(CH₂)_qCO₂R⁶;
- 20 R⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, aryl, -CH₂(1H-imidazol-4-yl), -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), -CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl), or -CH₂(3-pyridyl);
- W is CO₂R⁶, -CONH₂, -CONHOH, 5-tetrazole, or -CONR^{6b}CHR^{7b}CO₂R⁶;
- R⁶, R^{6a}, R^{6b}, R⁷, R^{7a}, and R^{7b} are each, independently, hydrogen, alkyl of 1-6 carbon atoms, or aryl;
- 25 Z¹ and Z² are each, independently, hydrogen, halogen, CN, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, cycloalkyl of 3-8 carbon atoms, nitro, amino, -NR¹R^{1a}, -NR¹COR^{1a}, cycloalkylamino of 3-8 carbon atoms, morpholino, or OR⁸, or Z¹ and Z² may be taken together as a diene unit
- 30 having the formula -CH=CR⁹-CR¹⁰=CH-;

R⁹ and R¹⁰ are each, independently, hydrogen, or alkyl of 1-6 carbon atoms;

p is 1 to 4;

q is 1 to 4;

or a pharmaceutically acceptable salt thereof.

5

3. The method of Claim 2 wherein the PTPase inhibiting compound is defined in Claim 2, wherein

A is hydrogen;

10 B and D are each, independently, halogen, alkyl of 1-6 carbon atoms, aryl, aralkyl of 6-12 carbon atoms, or cycloalkyl of 3-8 carbon atoms;

E is S or O;

X is hydrogen, halogen, alkyl of 1-6 carbon atoms, perfluoroalkyl of 1-6 carbon atoms, CN, alkoxy of 1-6 carbon atoms, aryloxy, arylalkoxy of 6-12 carbon atoms, arylsulfanyl;

15 Y is hydrogen, -NR¹R², or morpholine;

R¹ and R² are each, independently, hydrogen or alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, or aryl;

C is OR⁴;

R⁴ is hydrogen, alkyl of 1-6 carbon atoms, -CH(R⁵)W, or 5-thiazolidine-2,4-dione;

20 R⁵ is hydrogen, alkyl of 1-6 carbon atoms, aralkyl of 6-12 carbon atoms, aryl, -CH₂(3-1H-indolyl), -CH₂CH₂(1,3-dioxo-1,3-dihydro-isoindol-2-yl), or -CH₂CH₂(1-oxo-1,3-dihydro-isoindol-2-yl);

W is -CO₂R⁶, -CONH₂, -CONHOH, 5-tetrazole, -PO₃(R⁶)₂, or -CONR⁶CHR⁶CO₂R⁶;

25 R⁶ is hydrogen or alkyl of 1-6 carbon atoms;

Z¹ and Z² are taken together as a diene unit having the formula -CH=CH-H=CH-; or a pharmaceutically acceptable salt thereof.

4. The method of Claim 1 wherein the PTPase inhibiting compound is (2R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-dimethyl-phenoxy]-3-phenyl-propionic acid, or a pharmaceutically acceptable salt form thereof.

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5. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

- 5 (R)-2-[2,6-dibromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[2-bromo-4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-6-ethyl-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2, 6-dimethyl-phenoxy]-3-phenyl-propionic acid;
- 10 (R)-2-[4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-fluorophenoxy]-3-phenyl-propionic acid;
- [4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2, 6-diisopropylphenoxy]-acetic acid;
- or a pharmaceutically acceptable salt form thereof.

15

6. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

- (R)-2-[2-bromo-4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-6-sec-butyl-phenoxy]-3-phenyl-propionic acid;
- 20 (R)-2-[2-bromo-4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-6-isopropyl-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[2-bromo-4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-cyclopentyl-phenoxy]-3-phenyl-propionic acid;
- (R)-2-[4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-6-isopropyl-phenoxy]-3-phenyl-propionic acid;
- 25 (R)-2-[4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-cyclopentyl-phenoxy]-3-phenyl-propionic acid; or a pharmaceutically acceptable salt thereof.

7. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

- 30 (R)-2-[2,6-dibromo-4-(2,3-dimethyl-9-phenylsulfanyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-3-phenyl-propionic acid;

(R)-2-[2,6-dibromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-4-phenyl-butyric acid;

(S)-2-[2,6-dibromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-4-phenyl-butyric acid;

5 2-[2,6-dibromo-4-(9-bromo-3-methyl-2-morpholin-4-ylmethyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-3-phenyl-propionic acid;

(R)-2-[2,6-dibromo-4-(2,3-dimethyl-9-phenylsulfanyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-propionic acid; or a pharmaceutically acceptable salt thereof.

10 8. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

[2-bromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-nitro-phenoxy]-3-phenyl-propionic acid;

2, 6-dibromo-4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-phenol;

15 2-bromo-4-(9-bromo-2, 3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-6-nitro-phenol;

(R)-2-[2,6-dibromo-4-(9-bromo-2-diethylaminomethyl-3-methyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-3-phenyl-propionic acid;

20 (R)-2-[2,6-dibromo-4-(2,3-dimethyl-naphtho[2,3-b]furan-4-yl)-phenoxy]-3-phenyl-propionic acid; or a pharmaceutically acceptable salt thereof.

9. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

25 (2R)-2-[4-9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2,6-diisopropyl-phenoxy]-3-phenyl-propionic acid,

(R)-2-[4-(9-bromo-2-,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2,6-diethyl-phenoxy]-3-phenyl-propionic acid;

{{(2R)-2-[4-(9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2,6-dimethyl-phenoxy]-3-phenyl-propionylamino}-acetic acid;

30 {{(2R)-2-[4-(9-bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2,6-diethyl-phenoxy]-3-phenyl-propionylamino}-acetic acid;

(2R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-3-phenyl-propionic acid; or a pharmaceutically acceptable salt thereof.

10. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

- (2S)-2-[4-(9-Bromo-2-,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2,6-dimethyl-
 5 phenoxy]-3-phenyl-propionic acid;
 {(2R)-2-[4-(2,3-Dimethyl-naphtho[2,3-b]thiophen-4-yl)-2,6-diethyl-phenoxy]-3-
 phenyl-propionylamino}-acetic acid;
 (R)-2-[4-(9-Bromo-2-,3-dimethyl-naphtho[2,3-b]furan-4-yl)-2,6-diethyl-
 phenoxy]-3-phenyl-propionic acid;
 10 (R)-2-[2-Cyclopentyl-4-(2-,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-phenoxy]-
 propionic acid;
 (R)-2-[4-(9-Bromo-2-,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-cyclopentyl-
 phenoxy]-propionic acid; or a pharmaceutically acceptable salt thereof.

15 11. The method of Claim 1 wherein the PTPase inhibiting compound is selected from the group of:

- (R)-2-[4-(2-,3-Dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-ethyl-phenoxy]-3-
 phenyl-propionic acid;
 2-Bromo-4-(2-,3-dimethyl-naphtho[2,3-b]furan-4-yl)-6-ethyl-phenol;
 20 (R)-2-[2-Bromo-4-(2-,3-dimethyl-naphtho[2,3-b]furan-4-yl)-6-ethyl-phenoxy]-3-
 phenyl-propionic acid;
 (R)-2-[4-(9-Bromo-2-,3-dimethyl-naphtho[2,3-b]thiophen-4-yl)-2-propyl-
 phenoxy]-3-phenyl-propionic acid;
 (2R)-2-[4-(9-Bromo-2-diethylaminomethyl-3-methyl-naphtho[2,3-b]thiophen-4-
 25 yl)-2,6-diisopropyl-phenoxy]-3-phenyl-propionic acid;
 or a pharmaceutically acceptable salt thereof.

12. The method of Claim 1 wherein the biguanide agent is metformin, or a
 pharmaceutically acceptable salt thereof.

30

13. The method of Claim 1 wherein the optional sulfonylurea agent is selected from group of glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, or tolazamide, or a pharmaceutically acceptable salt form thereof.

14. A method of treating metabolic disorders mediated by insulin resistance or hyperglycemia in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a pharmaceutically effective amount of a PTPase inhibiting compound, as described in Claim 1, a pharmaceutically effective amount of a biguanide agent and, optionally, a sulfonylurea agent and or a pharmaceutically acceptable salt thereof.
15. The method of Claim 14 wherein the biguanide agent is metformin, or a pharmaceutically acceptable salt thereof.
16. The method of Claim 14 wherein the optional sulfonylurea agent is selected from group of glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, or tolazamide, or a pharmaceutically acceptable salt form thereof.
17. The method of Claim 14 wherein the PTPase inhibiting compound is (2R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-dimethyl-phenoxy]-3-phenyl-propionic acid, or (R)-2-[2,6-Dibromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-phenoxy]3-phenyl-propionic acid, or (R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-diethyl-phenoxy]-3-phenyl-propionic acid, or a pharmaceutically acceptable salt form thereof.
18. A method of modulating blood glucose levels in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a pharmaceutically effective amount of a PTPase inhibiting compound, as described in Claim 1, a pharmaceutically effective amount of a biguanide agent and, optionally, a sulfonylurea agent and or a pharmaceutically acceptable salt thereof.
19. The method of Claim 18 wherein the biguanide agent is metformin, or a pharmaceutically acceptable salt thereof.

20. The method of Claim 18 wherein the optional sulfonylurea agent is selected from group of glyburide, glyburide, glipizide, glimepiride, chlorpropamide, tolbutamide, or tolazamide, or a pharmaceutically acceptable salt form thereof.

5 21. The method of Claim 18 wherein the PTPase inhibiting compound is (2R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-dimethyl-phenoxy]-3-phenyl-propionic acid, or (R)-2-[2,6-Dibromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-phenoxy]3-phenyl-propionic acid, or (R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-diethyl-phenoxy]-3-phenyl-propionic acid, or a
10 pharmaceutically acceptable salt form thereof.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and:

- a) a pharmaceutically effective amount of metformin, or a
15 pharmaceutically acceptable salt thereof; and
- b) a pharmaceutically effective amount of a PTPase inhibiting compound of Claim 1, or a pharmaceutically acceptable salt form thereof; and
- c) optionally, a pharmaceutically effective amount of a sulfonylurea agent.

20

23. The pharmaceutical composition of Claim 22 comprising a pharmaceutically acceptable carrier or excipient and:

- a) a pharmaceutically effective amount of metformin, or a pharmaceutically acceptable salt thereof; and
- 25 b) a pharmaceutically effective amount of (2R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-dimethyl-phenoxy]-3-phenyl-propionic acid, or (R)-2-[2,6-Dibromo-4-(9-bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-phenoxy]3-phenyl-propionic acid, or (R)-2-[4-(9-Bromo-2,3-dimethyl-naphtho[2,3-*b*]thiophen-4-yl)-2,6-diethyl-phenoxy]-3-phenyl-propionic acid, or a pharmaceutically
30 acceptable salt form thereof; and
- c) optionally, a pharmaceutically effective amount of a sulfonylurea agent selected from the group of glyburide, glyburide, glipizide, glimepiride,

chlorpropamide, tolbutamide, or tolazamide, or a pharmaceutically acceptable salt form thereof.